Efficacy of Helical Tomography (HT) with Concurrent Chemoradiotherapy (CCRT) +Epidermal growth factor receptor (EGFR) inhibitor in Locally advanced nasopharyngeal carcinoma (LANC) patients invading carotid artery and risk of fatal bleeding

kun liu[1], Yang wang[1], Lin Ma[1], SM Yang[2], and Xinxin Zhang[1]

[1]Chinese PLA General Hospital
[2]Department of Otolaryngology Head and Neck Surgery, Institute of Otolaryngology, Chinese PLA General Hospital,

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Abstract

Abstract: Objectives: Are LANC patients with carotid artery invasion are at risk of massive neck hemorrhage after radiotherapy? Design: This retrospective study aims to assess the efficacy of HT with CCRT +/-EGFR inhibitor in LANC patients invading carotid artery and risk of fatal bleeding. Settings: Otolaryngology Head and Neck Surgery department in our hospital in China . Participants: Of 130 LANC patients with carotid artery invasion admitted to our hospital between January 2012 and September 2019. Main outcome measures: The 5-year survival rate of three degrees of the carotid artery invasion (<180°, 180°[?]IG<270deg, [?]270deg) . Univariate and Multivariate Cox regression analysis were used for survival correlation factors. Results: The incidence of fatal bleeding after radiotherapy was 2.3% (3/130). The primary site of the three cases were all the pharyngeal recess, with more than 270o carotid artery invasion. Patients with hemoglobin levels >110 g/L had a higher PFS, DMFS and OS than with that [?]110 g/L (P<0.05). Multivariate analysis showed that the EGFR inhibitor was an independent risk factor for PFS and DMFS, while the lowest hemoglobin level was an independent risk factor for OS. Conclusion: In LANC patients whose carotid artery invasion was <270o, HT combined with CCRT and EGFR inhibitor after induction chemotherapy had mild and tolerable side effects, better PFS and DMFS, with no massive hemorrhage. In patients [?]270o, diabetes with poor control or re-radiotherapy led to a higher risk of massive hemorrhage after radiotherapy.

Abstract:

Objectives:

Are LANC patients with carotid artery invasion are at risk of massive neck hemorrhage after radiotherapy?

Design:

This retrospective study aims to assess the efficacy of HT with CCRT +/-EGFR inhibitor in LANC patients invading carotid artery and risk of fatal bleeding.

Settings:

Otolaryngology Head and Neck Surgery department in China .

Participants:

Of 130 LANC patients with carotid artery invasion admitted to our hospital between January 2012 and September 2019.

Main outcome measures:

The 5-year survival rate of three degrees of the carotid artery invasion (<180°, 180°[?]IG<270deg, [?]270deg) . Univariate and Multivariate Cox regression analysis were used for survival correlation factors.

Results:

The incidence of fatal bleeding after radiotherapy was 2.3% (3/130). The primary site of the three cases were all the pharyngeal recess, with more than 270o carotid artery invasion. Patients with hemoglobin levels >110 g/L had a higher PFS, DMFS and OS than with that [?]110 g/L (P<0.05). Multivariate analysis showed that the EGFR inhibitor was an independent risk factor for PFS and DMFS, while the lowest hemoglobin level was an independent risk factor for OS.

Conclusion:

In LANC patients whose carotid artery invasion was <270o, HT combined with CCRT and EGFR inhibitor after induction chemotherapy had mild and tolerable side effects, better PFS and DMFS, with no massive hemorrhage. In patients [?]270o, diabetes with poor control or re-radiotherapy led to a higher risk of massive hemorrhage after radiotherapy.

Keywords : Locally advanced nasopharyngeal carcinoma, Carotid invasion, Helical tomography, Induction chemotherapy, Concurrent chemoradiotherapy, EGFR inhibitor, Massive neck hemorrhage, Risk factor

Key points:

1. This article is the first one to study the survival rate of different degrees of carotid artery invaded by nasopharyngeal carcinoma.
2. The incidence of fatal bleeding after radiotherapy was only 2.3% (3/130).
3. The circumference of tumor attachment to the artery and the disappearance of fat gaps were utilized to estimate the extent of carotid artery invasion , which was classified into three subtypes according to the involvement grade before therapy.
4. In LANC patients whose carotid artery invasion was <270o, helical tomotherapy combined with concurrent chemotherapy and EGFR inhibitor after induction chemotherapy had mild and tolerable side effects, better PFS and DMFS, with no massive hemorrhage.
5. In patients whose primary tumor was pharyngeal recess with carotid artery invasion [?]270o, diabetes with poor control or re-radiotherapy led to a higher risk of massive hemorrhage after radiotherapy.

1 Introduction

Nasopharyngeal carcinoma (NPC) is a malignant neoplasm with high radiosensitivity that has a unique etiology and geographic distribution. Due to the special anatomical location of the tumor, approximately 70% of newly diagnosed NPC cases are classified as locoregionally advanced disease, namely locally advanced nasopharyngeal carcinoma (LANC). NPC lesions often infiltrate the surrounding area, such as parapharyngeal space and internal carotid artery[1-2]. Concurrent chemoradiotherapy (CCRT), with epidermal growth factor receptor (EGFR) inhibitors, is an effective treatment option for LANC[3].

1.1 Objectives/Aims

Though radiotherapy killing tumor tissues, it may cause necrosis of surrounding tissues and exposure of the carotid artery, leading to fatal hemorrhage in certain patients with carotid artery invasion. No relevant studies have reported the therapeutic effects and associated risk factors for fatal massive hemorrhage in patients with LANC accompanied by carotid artery invasion. This retrospective study analyzed the therapeutic effects and associated risk factors in such patients.

1.2 Design

In clinical treatment, patients with nasopharyngeal carcinoma surrounded by carotid artery have occasionally died of neck bleeding after treatment. Is it related to the degree of carotid artery wrapping, or is it related

to the treatments ?

1.3 Participants

A total of 130 LANC patients (male 98, female 32; age range 10 to 74 years, mean age 48 years) with carotid artery invasion were recruited between January 2012 and September 2019 (Table 1). All patients had histologically proven stage III-IVA squamous cell carcinoma, largely non-keratinizing type, according to the most recent edition of the American Joint Committee on Cancer (AJCC) tumor/node/metastasis (TNM) classifications and prognostic stage groups . To rule out synchronous primary cancers and metastatic diseases, all patients were fully evaluated by positron emission tomography–computed tomography (PET-CT), magnetic resonance imaging (MRI) of the head and neck and fiberoscopic nasopharyngoscopy. Patients with synchronous primary cancers and/or metastatic disease were excluded. All patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and adequate renal, hepatic and bone marrow functions before chemoradiotherapy.

1.4 Main outcome measures

1.4.1 Treatments

Chemotherapy and EGFR inhibitor therapy

Two to four cycles of induction chemotherapy followed by concurrent chemoradiotherapy were given to all patients. EGFR-positive patients received Nimotuzumab, while EGFR-negative patients received Cetuximab (Table 2). All patients received oral mucositis prophylaxis followed by conventional mucositis treatment combined with quinolone antibiotics [4].

Radiotherapy

Helical tomotherapy (HT) was delivered once daily, 5 days per week, as previously described [5]. In brief, the planning dose at D95 (dose received by 95% of the target volume) was set at 67.5 grays (Gy) for the planning gross target volume of the primary tumor (pGTVnx) and the planning gross target volume of the metastatic lymph node (pGTVnd). The planning target volume (PTV) was set at 60 Gy and the PTV2 was set at 54 Gy in 30-33 fractions. No more than 5% of PTV volume received more than 110% of the prescribed dose. Dose-volume constraints for organs at risk (OARs) were set as follows: (1) parotid gland V30 <50% or Dmean [?]28 Gy; (2) brainstem Dmax [?]54 Gy; (3) spinal cord Dmax [?]45 Gy; (4) optic nerve Dmax [?]54 Gy; (5) temporo-mandibular joint Dmax [?]60 Gy; and (6) lens Dmax [?]5 Gy. HT plans were developed for a field width of 2.5 cm, a pitch of 0.30–0.38, and a modulation factor equal to 2.0–3.0. During radiation therapy, patients underwent megavoltage computed tomography (MVCT) imaging at least once each week to verify patient setup. The imaging frequency was determined by the magnitude of setup errors from initial daily scans. Carotid radiotherapy dose was the same among different groups.

1.4.2 Dose modifications

The cetuximab dose was reduced if a patient experienced an uncontrollable and persistent grade 2 acne-like rash. Chemotherapy doses and regimens were adjusted based on the severity of myelosuppression, hepatic and renal function and drug sensitivity. For example, carboplatin was administered instead of cisplatin if grade 1 renal toxicity was caused by cisplatin.

1.4.3 Radiographic evaluation

Axial scans of the neck obtained using contrast-enhanced MRI were reviewed by a radiologist. The circumference of tumor attachment to the artery and the disappearance of fat gaps were utilized to estimate the extent of carotid artery invasion [6], which was classified into three subtypes according to the involvement grade (IG) (Fig. 1-A-C) as follows before therapy:

(1) Low-involvement: the tumor invaded and/or contacted less than 180o of the carotid artery.

(2) Mid-involvement: the tumor invaded and/or contacted more than 180o but less than 270o of the carotid artery.

(3) High-involvement: the tumor invaded and/or contacted more than 270o of the carotid artery.

(Fig. 1-A-C)

The MRI maps before (Fig.1-D) and after (Fig.1-d) induction chemotherapy

1.4.4 Follow up

Follow-up examinations were scheduled for patients according the following arrangements: every 3 months in first year, every 4 months in second and third year, every 6 months in fourth and fifth years and then yearly until recurrence or death. Endpoints for this clinical trial were similar to those in our previous study [7]. Acute and late toxicities were graded according to the National Cancer Institute—Common Terminology Criteria for Adverse Events (CTCAE), version 5.0, and the Radiation Therapy Oncology Group (RTOG) Late Radiation Morbidity Scoring Criteria [8], respectively.

1.5 Ethical considerations

This research abides by international and national regulations in accordance with the Declaration of Helsinki. The studies involving human participants were reviewed and approved by the Ethics Committee of our Hospital. All patients provided written informed consent before being included in this study (patients under 16 years old were obtained from a parent or guardian for participants) .

1.6 Data Analysis

Data were analyzed by SPSS 24.0 statistical software (IBM Corporation, Armonk, NY, USA). 95% confidence intervals (CIs) were calculated for means and percentages. Curves of PFS, DMFS, LNRFS, LRFS, NRF and OS were estimated with the Kaplan–Meier method (GraphPad Prism 8.0.1). Group frequency data were examined using Chi-squared tests. Multivariate Cox regression analysis and Log-rank tests were used for survival correlation factors and inter-group curve comparisons, respectively.

2 Results

In the present study, 140 consecutive patients were screened for eligibility and 130 patients were enrolled in the clinical trial. Ten patients were excluded (4 were lost to follow-up and 6 were unbearable to side effects during concurrent chemoradiotherapy). Patients were stratified into 3 groups based on the degree of carotid artery involvement: <180o, n=37; 180o[?]IG<270o, n=32; and [?]270o, n=61.

Three patients whose primary tumor located in the nasopharyngeal recess and carotid artery invasion [?]270deg died of massive neck hemorrhage (Table 3; Fig.2).They were confirmed by repeated nasal endoscopy (gray-white necrotic material) and MRI enhancement of nasopharynx (gray-black necrotic material, non-neoplastic tissue, T1 phase is low signal, T2 phase is slightly high signal) prior to hemorrhage.No radiation-induced carotid pseudoaneurysms were confirmed by DSA.

The median follow-up time was 25 months (range 5-97 months). During the follow-up period, 20 patients died, 22 patients progressed (including 3 patients with recurrence, 2 with cervical lymph node metastasis, 16 with distant metastasis, and 1 with secondary primary cancer). The overall 5-year survival rates were PFS=75.2%, DMFS=76.8%, LNRFS=90.0%, LRFS=93.9%, NRFS=95.8% and OS=87.2% (Fig.3-1).

Univariate analysis showed that gender, age, pathological type and degree of carotid artery involvement were not significantly associated with survival. Clinical stage, induction chemotherapy regimen, concurrent chemotherapy regimen and EGFR inhibitors were significantly associated with PFS and DMFS ($P<0.05$). Hemoglobin levels during radiotherapy were significantly associated with DMFS, PFS and OS ($P<0.05$) (Supplementary Table 1).

Multivariate analysis showed that EGFR inhibitor was an independent prognostic factor for DMFS and PFS ($P<0.05$). Hemoglobin level during radiotherapy was an independent prognostic factor for OS ($P<0.05$)

(Supplementary Table 2; Fig3-2˜4).

Comparison of three degrees of the carotid artery invasion (<180deg, 180deg[?]IG<270deg, [?]270deg) suggested that the 5-year PFS was 82.3%, 72.4% and 59.5%, respectively; 5-year DMFS was 85.8%, 78.0% and 77.1%, respectively; 5-year LNRFS was 95.8%, 90.4% and 77.1%, respectively; 5-year LRFS was 95.8%, 100% and 77.1%, respectively; 5-year NRFS was 100%, 90.4% and 100%, respectively; and 5-year OS was 92.9%, 85.2% and 78.0%, respectively (Supplementary Fig.1-6).

Acute toxicities

All possible side effects were documented for each patient. Acute toxic effects were very mild and did not reach grade 4. The most common grade 1-2 toxicities included oropharyngeal mucositis, RT-related dermatitis, xerostomia and pharyngo-esophagitis, which were less severe than those of intensity-modulated radiation therapy (IMRT) (Supplementary Table 3). Acute toxicities were significantly improved 1 month after radiotherapy compared to those observed at the end of radiotherapy. Some patients treated with CCRT showed different degrees of bone marrow toxicity. After full radiotherapy, patients' average weight loss was 10.6%, varying from 0% to 20.4 %. Through the analysis between groups, there is no statistically significant side effect among the degree of carotid artery invasion.

3 Discussion

According to the National Comprehensive Cancer Network (NCCN), carotid artery invasion is a sign of poor prognosis, such as oral cavity cancer, P16¯oropharyngeal cancer, laryngeal cancer, hypopharyngeal cancer other than nasopharyngeal cancer. MR images were used to predict carotid artery invasion [9]: circumferential involvement of 270deg or less of the wall meant no invasion, and more than 270deg meant wall invasion. Based on our comparison of the survival rates in three degrees of carotid artery invasion (<180deg, 180deg[?]IG<270deg, and [?]270deg), although the difference was not statistically significant, it showed that the survival rate tended to decrease with an increase degree of invasion. However, patients with LANC with carotid artery invasion have a better prognosis, compared with other head and neck tumors. In this study, 130 LANC patients with carotid artery invasion were treated with induction chemotherapy followed by CCRT +- an EGFR inhibitor. Five-year survival rates were: PFS=75.2%; DMFS=76.8%; LNRFS=90.0%; LRFS=93.9%; NRFS=95.8% and OS=87.2%. Side effects were mild and well-tolerated; survival rates were similar to those observed in other studies [10-11].

Shen C et al. [12] showed that anemia is closely related to tumor hypoxia, which may lead to tumor resistance to radiotherapy and treatment failure. In this study, we found that the 5-year OS of patients with the lowest hemoglobin levels ([?]110 g/L) was significantly lower than that of patients with hemoglobin levels >110 g/L during radiotherapy. Therefore, we believe that patients should actively monitor and treat anemia.

Other studies have shown that patients whose primary tumor located in the pharyngeal recess, and who experienced inflammation and an opening incisor tooth distance <1 cm, had a greater probability of fatal bleeding after radiotherapy [13]. Yamazaki et al. [14] and Cheng et al. [15] believed that the pharyngeal recess is part of the petrosal region of the internal carotid artery where the tumor easily invades the internal carotid artery and surrounding bone. If the pharyngeal recess infected, the surrounding tissues may become necrotic, which may cause rupture of the internal carotid artery and fatal bleeding. Similarly, the primary site of the three cases were all the pharyngeal recess, with more than 270 o carotid artery invasion and restricted mouth opening.

Fatal bleeding is common in previous studies, Zheng et al. [16] found that 1.5% of nasopharyngeal carcinoma patients with IMRT experienced fatal bleeding. Wu et al.[13] showed that 52.9% (45/85) of such patients (stage I-IV) occurred fatal bleeding, with 20 patients died. In our study, all patients were stage III-IV, 32 cases with carotid artery invasion <180deg and 37 cases with 180deg[?]IG<270deg, no patients suffered fatal neck hemorrhage.

Sixty one patients with carotid artery invasion [?]270deg, among whom three patients died of neck hemorrhage, the overall incidence was only 2.3% (3/130), which was attributable to nasopharyngeal necrosis (2

of whom were diabetics and 1 received re-radiation after recurrence). Most scholars believe that radiation, trauma and infection cause nasopharyngeal necrosis [14]. Re-radiation increases the risk of necrosis of the nasopharynx and neck hemorrhage [17]. The 2 diabetics had uncontrollable infection with local necrosis. The patient who received re-radiation was exposed to a cumulative radiation dose of 137.5 Gy and developed osteoradionecrosis of the nasopharynx seven months after radiotherapy. Another patient with the primary site of the nasopharyngeal wall was treated with surgery after recurrence, and he survived without fatal bleeding. Surgery may be a better option than re-radiation for patients with carotid artery invasion [?]270deg who experience recurrence.

In our study, 127 patients without massive hemorrhage benefited from the application of induction/concurrent chemotherapy and HT. Induction chemotherapy can reduce tumor load, enlarge the space between the carotid artery and the tumor body and produce a greater safety margin, thereby reducing damage to important tissues and organs caused by radiotherapy. Dionisi et al. [18] showed that CCRT could further shrink the tumor body, accelerate blood supply to surrounding tissues, and reduce the incidence of mucosal necrosis. HT has many dosimetric advantages, such as delivering a more precise dosage to the target tissue(s) and reducing radiation exposure to critical surrounding organs, thereby improving local control with less radiation damage [19]. In addition, multivariate analysis showed that use of an EGFR inhibitor was an independent prognostic factor for PFS and DMFS. Previous studies have shown that adding CTX/NTZ to CCRT may improve OS, DFS and DMFS [20-24], which is consistent with our results. EGFR inhibitors also have been shown to have significant anti-proliferation, pro-apoptosis and anti-angiogenesis effects, which may further control the recurrence of tumors and improve the sensitivity of tumors to radiotherapy and chemotherapy [25].

In conclusion, 130 patients with LANC surrounding the carotid artery were treated with a comprehensive treatment regimen, 95.7% of the patients successfully completed the entire courses, producing desirable outcomes and a low incidence of fatal hemorrhage. Improved outcomes may be possible with the application of new proton and other radiotherapy technologies and new PD-1 immuno-targeted drugs in patients with nasopharyngeal carcinoma. The primary site located in the pharyngeal recess with more than 270 o carotid artery invasion and restricted mouth opening, especially diabetics, should actively control blood glucose levels and prevent infection. Nasopharyngeal necrosis should be actively treated by antibiotics and hyperbaric oxygen, removing by oxygen nasal endoscope regularly.

Abbreviations: Arrowheads indicate the ICA; LANC, Locally advanced nasopharyngeal carcinoma; MRI, magnetic resonance imaging; ICA, internal carotid artery; T1WI, T1-weighted imaging

EGFR, epidermal growth factor receptor inhibitor; PFS, progression-free survival; DMFS, distant metastasis-free survival; LNRFS, local nodal recurrence-free survival; LRFS, local recurrence-free survival; NRFS, nodal recurrence-free survival; OS, overall survival

T: docetaxel; P: cisplatin; F: 5-fluorouracil; G: Gemcitabine; D: Doxorubicin

HR3, Nimotuzumab; C-225, Cetuximab; HT, helical tomography

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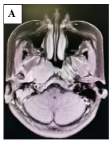

Fig.1-A The tumor invaded and/or contacted less than 180° of the carotid artery

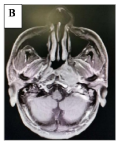

Fig.1-B The tumor invaded and/or contacted more than 180° but less than 270° of the carotid artery

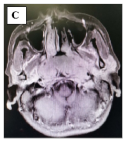

Fig.1-C The tumor invaded and/or contacted more than 270° of the carotid artery

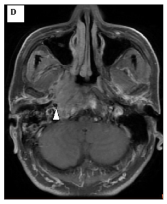

Fig.1-D The MRI of one patient whose tumor invaded and/or contacted more than 270° of the carotid artery before induction chemotherapy

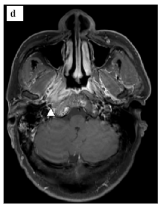

Fig.1-d The MRI of one patient whose tumor invaded and/or contacted more than 270° of the carotid artery after induction chemotherapy

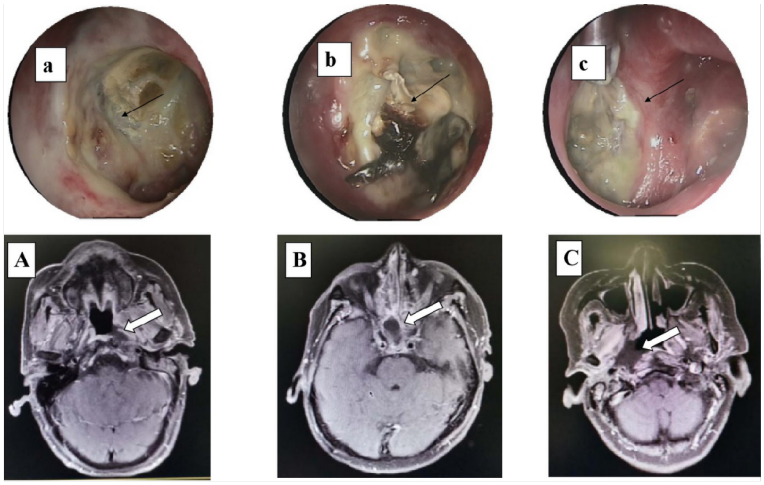

Fig.2 The nasal endoscope and MRI of three patients whose primary tumor located in the nasopharyngeal recess and carotid artery invasion ≥270° died of massive neck hemorrhage after radiotherapy

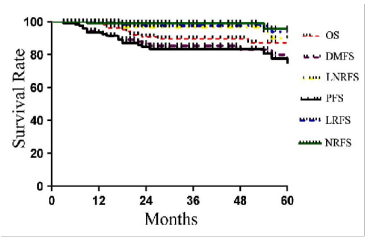

Fig.3-1 The 5-year survival rates of all patients

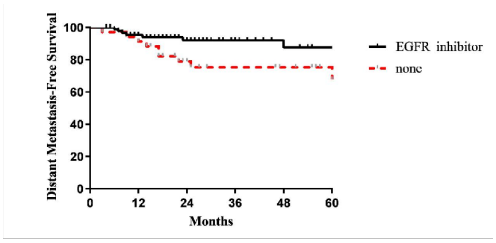

Fig.3-2 Comparison of DMFS in patients with EGFR inhibitor or not(P＜0.05）

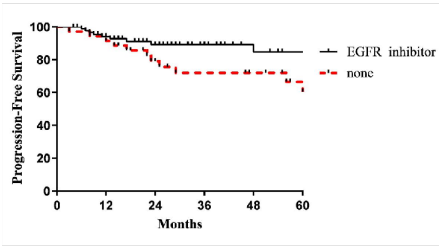

Fig.3-3 Comparison of PFS in patients with EGFR inhibitor or not(P＜0.05）

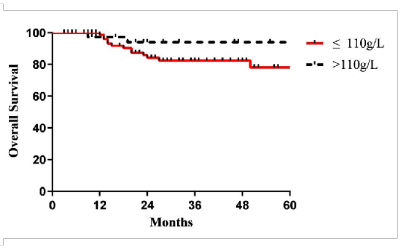

Fig.3-4 Comparison of OS in patients with hemoglobin levels >110 g/L and hemoglobin levels ≤110 g/L (P<0.05)

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Table 2.doc available at https://authorea.com/users/740634/articles/713410-efficacy-of-helical-tomography-ht-with-concurrent-chemoradiotherapy-ccrt-epidermal-growth-factor-receptor-egfr-inhibitor-in-locally-advanced-nasopharyngeal-carcinoma-lanc-patients-invading-carotid-artery-and-risk-of-fatal-bleeding

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Table 3.doc available at https://authorea.com/users/740634/articles/713410-efficacy-of-helical-tomography-ht-with-concurrent-chemoradiotherapy-ccrt-epidermal-growth-factor-receptor-egfr-inhibitor-in-locally-advanced-nasopharyngeal-carcinoma-lanc-patients-invading-carotid-artery-and-risk-of-fatal-bleeding